Animal models of drug abuse - towards new neuronal mechanisms and high translational value

Reverse-translational models of drug relapse: behavior, pharmacology, circuits, and treatment implications

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The rat reinstatement model of drug relapse is nearly 40 years old. The goal of research using this model has been to identify new treatments. However, research using the reinstatement model in its traditional form has not led to FDA-approved medications for relapse prevention. This state-of-affairs is not unique to the reinstatement model, but it is an increasing source of disappointment, and it calls for a regrouping. In our lab, we have regrouped by developing procedures that mimic successful human treatments: opioid agonist maintenance, contingency management, and community-reinforcement approach. In the lecture, I will describe our "reverse translation treatment approach" and describe how we use it to identify new relapse-related brain circuits and relapse prevention medications.

Venniro, M., Zhang, M., Caprioli, D., Hoots, J.K., Golden, S.A., Heins, C., Morales, M., Epstein, D.H. & Shaham, Y. (2018) Volitional social interaction prevents drug addiction in rat models. Nature neuroscience, 21, 1520-1529.

Venniro, M., Banks, M.L., Heilig, M., Epstein, D.H. & Shaham, Y. (2020) Improving translation of animal models of addiction and relapse by reverse translation. Nature reviews. Neuroscience, 21, 625-643.

Biobehavioural basis of the flexible inflexibility that characterises maladaptive drug-seeking at relapse

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The inflexible pursuit of drug-seeking and tendency to relapse that characterize addiction have been associated with the recruitment of the dorsolateral striatum-dependent habit system. However, the mechanisms by which the resulting maladaptive drug-seeking habits contribute to relapse have not been elucidated. During this presentation I will show that a long history of cocaine-seeking invigorated by response-produced drug-paired cues specifically results, at a time it is mediated by the habit system, in aberrant drug-seeking at relapse. This exacerbated relapse is underpinned by a transient engagement of the dorsomedial striatum-dependent goal-directed system promoted by the inability to enact seeking habits during abstinence, but not the lack of the drug. These results shed light on the psychological and neural basis of relapse.

Amygdalar silent synapses in appetitive learning and addiction

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Silent synapses are excitatory connections that possess one of the two main type of glutamate receptors – NMDA receptors, while AMPA receptors are either absent. They do not participate in the basal synaptic transmission, hence the term "silent". Yet they can be easily recruited in LTP processes, such as learning, where they acquire AMPA receptors, and become fully functional contacts that strengthen the excitatory connection. In my talk, will describe the phenomenon of silent synapses induction in cocaine addiction models and present our latest research on the function of silent synapses in amygdala in appetitive learning and the development of alcohol addiction.

Stefaniuk, M., Beroun, A., Lebitko, T., Markina, O., Leski, S., Meyza, K., Grzywacz, A., Samochowiec, J., Samochowiec, A., Radwanska, K. & Kaczmarek, L. (2017) Matrix metalloproteinase-9 and synaptic plasticity in the central amygdala in control of alcohol-seeking behavior. Biol Psychiatry, 81, 907-917.

ARC in the amygdala prevents compulsive alcohol seeking

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Alcohol use disorder is a chronic psychiatric disorder characterized by the compulsion to seek and consume alcohol. This maladaptive behavior is driven by cellular and molecular adaptations that are still poorly understood. Using advanced tools, such as RNA sequencing, local genomic manipulation with the CRISPR/Cas9 system in vivo and behavioral analysis of the mice in IntelliCages, we looked for molecular markers that regulate compulsive alcohol drinking. We discovered that ARC protein expression in the amygdala during alcohol withdrawal prevents compulsive response to alcohol-predicting cues.